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ORIGINAL ARTICLE

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Biochemical markers of bone turnover may predict progression to osteoporosis in osteopenic women: the JPOS Cohort Study

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Abstract We evaluated the value of bone turnover markers, including osteocalcin (OC) and bone-specific alkaline phosphatase in the serum, and type I collagen C-terminal telopeptide and free and total deoxypyridinoline (tDPD) in the urine of fasting patients, in an attempt to predict which osteopenic women [i.e., those with ≥70% and <80% of the young adult mean (YAM) bone mineral density (BMD)] would progress to the osteoporosis level of BMD (<70% of YAM). Of the 1153 women without defects in bone metabolism who completed the 3-year follow-up, 147, 161, and 144 women were judged by dual X-ray absorptiometry to be osteopenic from baseline measurements of BMD in the spine (LS), hip (TH), and distal radius (DR), respectively. Progression to the osteoporotic level of BMD was noted for 23.8%, 16.1%, and 12.5% of the subjects with osteopenia of the LS, TH, and DR, respectively, while most of them were in the lower half of the osteopenic level of BMD at baseline. Among the subjects in this lower-level osteopenia category, a significantly higher OC level was observed for the subjects with osteoporosis progression at the LS than those without. The subjects with progression at DR showed a significantly higher tDPD level. The association between OC level and disease progression remained unchanged after adjustments for age, body size, and BMD at baseline. The subjects in the upper one-third category of OC levels showed a 6.4 fold greater risk of progression at LS (95% confidence interval, 1.8–23.1) compared with those in the lower one-third category after the adjustments for age, body size, and BMD at baseline. Receiver operating characteristics analysis showed that the area under the curve was 0.716 for the OC level in the prediction of osteoporosis progression at LS. The levels of OC and tDPD may be useful in predicting which osteopenic women will progress to osteoporosis.

Key words biochemical markers of bone turnover · bone mineral density · cohort study · deoxypyridinoline · Japanese women · osteocalcin · osteopenia · osteoporosis · progression · random sample

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Introduction

The goal of osteoporosis management is the prevention of fragility fractures. In recent years, we have seen the development of potent drugs against osteoporosis, such as alendronate, risedronate, and raloxifene, which reduce the risk of fractures by about half [1]. A major problem that persists is the identification of those patients who will derive optimal benefit from drug therapy.

The International Osteoporosis Foundation [2] recommends that drug therapy is initiated after diagnosis of

osteoporosis according to the World Health Organization (WHO) criterion of bone mineral density (BMD) >2.5 SD below the young adult mean (YAM) BMD [3]. According to the guidelines for osteoporosis management published by the National Osteoporosis Foundation (NOF), drug therapy should be offered to a woman with strong risk factors and a BMD T-score below –2.0 [4]. The Canadian Task Force on Preventive Health Care recommends treatment for a woman aged 65 years or older with a BMD T-score below –2.0 [5].

According to the criteria set by the Japanese Society for Bone and Mineral Research (JSBMR), people with BMD <70% of YAM are judged to be osteoporotic and those with BMD ≥70% and <80% of YAM are designated as osteopenic [6]. This diagnostic criterion for osteoporosis acts also as an intervention threshold for drug therapy. The JSBMR criterion for osteoporosis is almost equivalent to the WHO criterion for the lumbar spine, and is more conservative as a threshold for drug therapy than the NOF guideline [4] or the Canadian recommendation [5]. The risk of fracture for osteopenic women is estimated to be at least 1.5 fold greater than that for women with normal BMD [7] and may not be left without any intervention. However, alteration of the treatment threshold from the osteoporotic level to the osteopenic level would cause dramatic increase in the number of women receiving drug therapy and would involve substantial cost to the Japanese healthcare system. For more cost-effective management of osteopenic women, it is desirable to know which osteopenic women will progress to the osteoporotic level in the near future. Biochemical markers of bone turnover may be useful for this purpose.

Many studies have examined postmenopausal women for associations between the levels of biochemical markers of bone turnover and subsequent changes in BMD of the forearm [8–12], spine [13–18], or hip [19,20]. It has also been reported for Japanese women that the levels of several biochemical markers of bone turnover are significantly related to BMD changes in perimenopausal women [21] and more modestly associated in women aged 40 through 79 years [22]. However, these assays are currently considered as not being sufficiently accurate to be used for the prediction of bone loss on an individual basis [23,24].

Previous studies, including ours [21], set the outcome as the change or rate of change in BMD. The limitations of these studies are that (1) changes in BMD are not always predictive of whether a subject will reach the intervention threshold, because a subject with high BMD at baseline would be unlikely to exceed the threshold even with a relatively high rate of change in BMD, and (2) the relationship between the levels of markers and change in BMD may not be linear, so that the usual regression or correlation analysis may not show the real relationship. Therefore, in the present study, we defined the outcome as a dichotomous variable, i.e., whether an osteopenic woman would progress to the osteoporotic level of BMD in the following 3 years, and we aimed to determine which biochemical markers of bone turnover could be used to predict progression. We used the data from the Japanese Population-based Osteoporosis (JPOS) Study, in which Japanese women aged 15–79 years were randomly selected from the general population [25,26] and presented for follow-up after 3 years [21].

Subjects and methods

Setting

This study was performed as a part of the epidemiological JPOS Cohort Study [21], in which 50 women were randomly selected from each of 5-year age groups covering ages from 15 to 79 years, based on resident registrations in three municipalities from different areas of Japan, i.e., Nishi-Aizu Town, located in a mountainous area of Honshuu Main Island, Sanuki City (formerly Sangawa Town), in Shikoku facing the Seto Inland Sea, and Miyakojima City (formerly Hirara City) in Okinawa, the southern island in the subtropical zone. Details of this study are provided elsewhere [21,26].

Subjects

Of the 1950 women selected at baseline, 1651 (84.7%) completed the baseline study, which comprised measurements of biochemical markers of bone turnover, BMD, and body size, as well as interviews. Excluded subjects (n = 147) included those with current or previous disease affecting bone metabolism, such as amenorrhea, oligomenorrhea, bilateral oophorectomy, diseases of the parathyroid gland, rheumatoid arthritis, diabetes mellitus, cancer, and stroke, as determined during the interviews or in laboratory tests, which included assays for serum calcium, inorganic phosphorus, parathyroid hormone, and 1,25-dihydroxy vitamin D, as well as the biochemical markers of bone turnover described below, those who had received drugs that affect bone turnover, such as calcium, estrogens, vitamin D, calcitonin, bisphosphonates, and glucocorticoids, and those who did not submit blood or urine samples. The remaining 1504 (77.1% of the total) women were invited for a follow-up study 3 years after the baseline, which consisted of the same BMD and body size measurements and similar interviews as in the baseline survey. In all, 1285 women (85.4% of the subjects eligible for follow-up) completed the follow-up survey, and 132 women were further excluded from the study because they were found to have incident diseases that affected bone metabolism and/or had initiated drug regimens (as previously described) during the follow-up period. From the remaining 1153 women, we selected osteopenic subjects at baseline according to the JSBMR criterion and used these data for the main analyses.

Written informed consent for all the study procedures was obtained from each subject in advance. The study protocol was approved by the Ethical Committee of the Kinki University School of Medicine.

Biochemical markers of bone turnover

The methods for measuring biochemical markers of bone turnover have been described previously [26]. Briefly, we measured at baseline the serum levels of osteocalcin (OC) and bone-specific alkaline phosphatase (BAP), and the urinary levels of type I collagen cross-linked C-terminal telopeptide (CTX) and the free (fDPD) and total (tDPD) forms of immunoreactive deoxypyridinoline after overnight fast using commercially available kits according to the manufacturers' protocols.

Serum OC (nmol/l) was measured by a two-site immunoradiometric assay (IRMA) (BGP IRMA Kit; Mitsubishi Kagaku Iatron, Tokyo, Japan) with a sensitivity of 0.17 nmol/l [27]. Serum BAP (ng/ml) was measured by IRMA (Tandem-R Ostase; Hybritech, San Diego, CA, USA) with a sensitivity of 0.1 ng/ml [28]. CTX (μg/l) was measured by an enzyme-linked immunosorbent assay (ELISA) (CrossLaps ELISA; Osteometer A/S, Rødovre, Denmark) with a detection limit of 0.5 μg/l [29]. Urine fDPD (nmol/l) was determined by ELISA (Pyrilinks-D; Metra Biosystems, Mountain View, CA, USA) with a minimal detection limit of 1.1 nmol/l [30]. Urine tDPD (nmol/l) was measured by the method used for fDPD after hydrolysis of the urine specimen, with a minimal detection limit of 11 nmol/l. All the values obtained for the urinary markers were corrected for creatinine (Cr) concentration (mmol Cr/l).

Intraassay precision, as represented by the coefficient of variation (CV), was 8.0%, 6.9%, 5.0%, 5.6%, and 6.8%, and interassay precision during the 9 months of the baseline study period was 14.2%, 11.9%, 14.5%, 12.6%, and 16.8% for OC, BAP, CTX, fDPD, and tDPD, respectively. Time trends of measured markers for the control specimens did not deviate significantly from zero throughout the study.

Bone mineral density measurement

BMD was measured by dual X-ray absorptiometry (DXA) at the lumbar spine (L2–L4) and right hip in a posteroanterior projection (QDR4500A; Hologic, Bedford, MA, USA) and at the distal forearm of the nondominant side (Norland pDEXA; Norland-Stratec, Fort Atkinson, WI, USA), as described previously [25]. Subjects with a history or incident involvement of fractures or bone disease in the right hip or nondominant forearm were scanned on the other side. Morphometry of the spine was performed with the QDR4500A at the same time to exclude subjects with fractures of the lumbar spine from the analysis of BMD. Densitometric data for the spines of subjects with vertebral fractures [31], those with fourth-grade osteophytes, as defined using Nathan's classification [32], or those with hip or forearm deformities in regions of interest were not used in the analysis. These procedures were performed in the baseline and follow-up studies. All measurements of the spine and hip were made with a single scanner throughout the study, which was installed in a mobile test room in a large vehicle. The forearm BMDs were also measured with two scanners that were closely calibrated with each other. The BMD values of the spine (LS), total hip (TH), and distal one-third site of the radius (DR) were used in the analysis. The short-term precision (CV) values of the BMD measurements in vivo were 1.2%, 1.2%, and 1.2% for LS, TH, and DR, respectively. No significant drift in BMD was observed for the spine or forearm phantom throughout the follow-up period, and the CV values in vitro were 0.48% and 0.34%, respectively.

The diagnosis of osteopenia according to the JSBMR criterion was performed independently at each skeletal site of the LS, TH, and DR, with 147, 161, and 144 osteopenic women, respectively, being identified at these sites. When the BMD of a subject at follow-up decreased to the osteoporotic level according to the JSBMR criterion, the subject was judged to have progression.

Interviews

The subjects responded to a questionnaire that included questions as to menstrual history and its present status, history and present involvement of gynecological and other diseases or medications that might affect bone metabolism, and lifestyle factors, such as smoking, drinking, exercise, and dietary habits. Each subject was asked to fill out the questionnaire before the baseline visit. Detailed interviews were conducted by trained nurses and dietitians during the baseline survey based on the responses provided in the questionnaires, and similar interviews were performed at the follow-up.

Body size measurements

Height (cm) and weight (kg) were measured using an automatic scale (TK-11868h; Takei Kagaku, Tokyo, Japan) in each survey period. The body mass index (BMI; in kg/m^2) was calculated as the weight (kg) divided by the height (m) squared.

Statistics

The geometric mean and SD were used for the OC, CTX, fDPD, and tDPD values, because they followed a logarithmic normal distribution. Comparisons of the mean values between two groups were performed using the Student's *t* test. A trend of the incidence rate of progression with increasing levels of bone turnover markers was tested by the Cochran–Armitage trend test. The odds ratio (OR) for the progression was calculated by multivariate logistic regression. The area under the curve (AUC) in the receiver operating characteristics (ROC) analysis was used as an index of validity of the bone turnover markers for predicting progression. All the statistical calculations were performed using the SAS system for personal computers (release 6.12; SAS Institute, Cary, NC, USA).

Results

Subject characteristics

Table 1 shows the basic characteristics of the osteopenic subjects at the LS, TH, and DR. The prevalence rate of osteopenia at baseline ranged from 12.5% to 14.0% depending on the skeletal sites measured. The subjects diagnosed as osteopenic at TH had significantly lower bodyweights and had lower BMI values than those with osteopenia at the other sites. There was no difference in the levels of biochemical markers of bone turnover among the three osteopenic groups.

Change in BMD categories

During the follow-up period, 23.8%, 16.1%, and 12.5% of the subjects with osteopenia at LS, TH, and DR at baseline, respectively, progressed to the osteoporotic level. Table 2 shows the changes in BMD categories during the follow-up period in the subjects with osteopenia, who are further divided into groups with higher and lower osteopenic levels of BMD at baseline. Most of the progressed subjects were originally in the lower osteopenic category. Therefore, we focused on the osteopenic subjects of this category, i.e., those with BMD ≥70% and <75% of YAM at baseline, in the following analyses for the prediction of osteoporosis progression.

Table 1. Basic characteristics of the subjects

	Skeletal site evaluated		
	Spine	Hip	Distal radius
Number of osteopenic subjects[a]	152	161	144
Prevalence of osteopenia:	13.2%	14.0%	12.5%
At baseline			
Age (years)	65.2 ± 7.5	67.2 ± 7.3	65.7 ± 6.6
Height (cm)	147.5 ± 5.1	147.0[b] ± 5.7	148.4 ± 4.8
Weight (kg)	52.5 ± 6.6	49.7[b] ± 6.5	54.2 ± 7.8
Serum OC (nmol/l)	1.42 ×/÷ 0.3	1.39 ×/÷ 0.4	1.36 ×/÷ 0.3
Serum BAP (ng/ml)	15.8 ± 6.8	15.9 ± 5.9	14.6 ± 5.4
Urinary CTX (mg/mmol Cr)	336.3 ×/÷ 0.5	326.5 ×/÷ 0.6	301.8 ×/÷ 0.5
Urinary fDPD (nmol/mmol Cr)	6.1 ×/÷ 0.4	5.9 ×/÷ 0.3	5.8 ×/÷ 0.3
Urinary tDPD (nmol/mmol Cr)	11.9 ×/÷ 0.4	11.6 ×/÷ 0.3	11.1 ×/÷ 0.4
BMD (g/cm^2)	0.766 ± 0.029	0.667 ± 0.025	0.564 ± 0.019
T-score	−2.0 ± 0.2	−1.7 ± 0.3	−2.7 ± 0.3
% of YAM	74.3 ± 2.8	75.2 ± 2.8	74.7 ± 2.5
At follow-up			
Height (cm)	147.0 ± 5.2	146.5 ± 5.7	147.9 ± 4.8
Weight (kg)	51.1 ± 6.8	48.3 ± 6.8	52.7 ± 8.0
BMD (g/cm^2)	0.751 ± 0.040	0.650 ± 0.036	0.552 ± 0.033
T-score	−2.6 ± 0.4	−2.2 ± 0.3	−3.2 ± 0.5
% of YAM	72.8 ± 3.8	73.3 ± 4.0	73.0 ± 4.3

Values connected with ×/÷ are geometric mean and SD; remaining values are arithmetic mean and SD

OC, osteocalcin; BAP, bone-specific alkaline phosphatase; CTX, type I collagen C-terminal telopeptide; tDPD and fDPD, total and free forms of deoxypyridinoline; BMD, bone mineral density; YAM, young adult mean BMD

[a] Osteopenia: BMD ≥70% and <80% of YAM

[b] Significant difference from other two groups at $P < 0.001$ by Student's t test with Bonferroni's adjustment for significance level

Source: Data from the Japanese Population-based Osteoporosis (JPOS) study

Table 2. Changes in bone mineral density (BMD) categories during the follow-up period defined relative to the young adult mean BMD (YAM)

Pattern of change in BMD categories		Number of subjects in each altered BMD category for:		
At baseline	At follow-up	Spine	Hip	Distal radius
≥75% and <80% of YAM Upper-level osteopenia	≥75% of YAM	38 (66.7%)	53 (63.1%)	33 (51.6%)
	≥70% and <75% of YAM	17 (29.8%)	31 (36.9%)	25 (39.1%)
	<70% of YAM	2 (3.5%)	0 (0%)	6 (9.4%)
≥70% and <75% of YAM Lower-level osteopenia	≥70% of YAM	62 (65.3%)	51 (66.2%)	62 (77.5%)
	<70% of YAM	33 (34.7%)	26 (33.8%)	18 (22.5%)

Source: Data from the JPOS Cohort Study

Table 3. Difference in baseline characteristics between the lower-level osteopenia subjects[a] who progressed to the osteoporosis level and those who did not

Variables at baseline	Spine			Hip			Distal radius		
	Progressed	Not progressed	*P* value[c]	Progressed	Not progressed	*P* value[c]	Progressed	Not progressed	*P* value[c]
Age (years)	63.8 ± 7.5	66.0 ± 7.6	0.1761	70.2 ± 6.4	66.7 ± 7.0	0.0356	65.4 ± 5.9	67.3 ± 6.6	0.2950
Height (cm)	148.3 ± 4.9	146.9 ± 5.5	0.2088	144.3 ± 6.6	147.0 ± 5.1	0.0435	149.6 ± 3.7	146.6 ± 5.0	0.0242
Weight (kg)	52.3 ± 5.9	52.5 ± 7.4	0.8990	48.4 ± 6.2	49.3 ± 6.8	0.5986	57.9 ± 7.6	52.1 ± 7.5	0.0044
BMD (g/cm^2)	0.744 ± 0.016	0.749 ± 0.015	0.1996	0.640 ± 0.120	0.646 ± 0.012	0.0621	0.548 ± 0.010	0.550 ± 0.011	0.3585
Serum OC (nmol/l)	1.63 ×/÷ 0.2	1.34 ×/÷ 0.3	0.0016	1.42 ×/÷ 0.4	1.35 ×/÷ 0.4	0.6020	1.47 ×/÷ 0.3	1.25 ×/÷ 0.3	0.0768
Serum BAP (ng/ml)	17.0 ± 5.2	14.8 ± 5.6	0.0575	17.2 ± 8.9	16.1 ± 5.9	0.5527	14.9 ± 4.0	13.8 ± 4.4	0.3344
Urinary CTX (mg/mmol Cr)	369.5 ×/÷ 0.5	308.9 ×/÷ 0.5	0.1050	322.2 ×/÷ 0.7	339.8 ×/÷ 0.6	0.7331	329.2 ×/÷ 0.6	275.5 ×/÷ 0.6	0.2453
Urinary fDPD (nmol/mmol Cr)	6.5 ×/÷ 0.3	6.0 ×/÷ 0.3	0.2001	5.9 ×/÷ 0.3	6.1 ×/÷ 0.2	0.7594	5.8 ×/÷ 0.3	5.7 ×/÷ 0.3	0.7978
Urinary tDPD (nmol/mmol Cr)	12.7 ×/÷ 0.4	11.0 ×/÷ 0.4	0.0982	12.1 ×/÷ 0.4	11.7 ×/÷ 0.3	0.7845	12.8 ×/÷ 0.3	10.4 ×/÷ 0.4	0.0461

Values connected with ×/÷ are geometric mean and SD; others are arithmetic mean and SD
BMD, bone mineral density; OC, osteocalcin; BAP, bone-specific alkaline phosphatase; CTX, type I collagen C-terminal telopeptide; fDPD and tDPD, free and total forms of deoxypyridinoline; YAM, young adult mean BMD
[a] Lower-level osteopenia was defined as BMD ≥70% and <75% of YAM
[b] Osteoporosis was defined as BMD <70% of YAM according to the Japanese Society for Bone and Mineral Research Criteria
[c] *P* value was calculated by Student's *t* test or by Welch's appropriate *t* test if the SDs differed significantly
Source: Data from the JPOS Cohort Study

Difference between subjects with and without progression

We compared the baseline characteristics of the subjects with BMD ≥70% and <75% of YAM with and without progression to osteoporosis (Table 3). No difference was noted in terms of age, height, or weight between those with and without progression at LS, although the level of OC was significantly higher in the subjects with progression. At TH, the subjects with progression were significantly older and shorter than those without progression, but they showed no other difference. The subjects with progression at DR had better physiques and higher levels of tDPD. The association between OC levels and progression at LS remained significant after adjustments for age, body size, and BMD at baseline.

Bone turnover markers and incidence of progression

The incidence rates of progression were compared among the lower osteopenic subjects, who were divided into three groups based on the tertile values for the biochemical markers of bone turnover at baseline (Table 4). Significantly higher rates of progression at LS were observed in the groups with higher levels of OC, BAP, and tDPD, but not in the groups with higher levels of CTX or fDPD. No association was noted between any marker level and progression at TH.

Multiple logistic regression models were used to obtain the OR for each tertile group of biochemical markers of

Table 4. Incidence rates of progression in the women with lower-level osteopenia[a] as classified according to the tertile values of the biochemical markers of bone turnover

Biochemical markers	Tertile groups	Incidence rate of progression at		
		Spine	Hip	Distal radius
OC	Lower	12.9%	30.8%	7.4%
	Middle	39.4%	44.0%	26.9%
	Upper	51.6%	26.9%	33.3%
	P for trend[b]	0.002	0.884	0.034
BAP	Lower	16.1%	36.0%	19.2%
	Middle	35.5%	33.3%	10.7%
	Upper	51.5%	32.0%	38.5%
	P for trend[b]	0.004	0.882	0.137
CTX	Lower	25.8%	24.0%	14.8%
	Middle	34.4%	50.0%	26.9%
	Upper	43.8%	26.9%	25.9%
	P for trend[b]	0.149	0.884	0.419
fDPD	Lower	32.3%	34.6%	15.4%
	Middle	21.9%	26.9%	28.6%
	Upper	50.0%	40.0%	23.1%
	P for trend[b]	0.149	0.692	0.622
tDPD	Lower	16.1%	29.2%	12.0%
	Middle	45.2%	33.3%	23.1%
	Upper	41.9%	37.5%	30.8%
	P for trend[b]	0.045	0.649	0.131

OC, osteocalcin; BAP, bone-specific alkaline phosphatase; CTX, type I collagen C-terminal telopeptide; fDPD and tDPD, free and total forms of deoxypyridinoline
[a] Lower-level osteopenia was defined as BMD ≥70% and <75% of the young adult mean BMD
[b] *P* for trend was calculated by the Cochran–Armitage trend test
Source: Data from the JPOS Cohort Study

bone turnover for progression with adjustments for age, height, weight, and BMD at baseline (Fig. 1). The subjects with the upper two-third OC levels (>1.41 nmol/l) had significantly elevated ORs for progression at LS and DR in comparison with those with the lower one-third OC levels. Similar but more modest tendencies were observed for tDPD (>11.0 nmol/mmol Cr) and for BAP (>16.4 ng/ml), but not for CTX or fDPD (data not shown). No association was observed between any of the bone turnover markers and progression at TH (data not shown).

Predictive value of bone turnover markers for osteoporosis progression

The ROC analyses of the OC and tDPD levels at baseline for progression at LS and DR were performed for the lower-level osteopenic women (Fig. 2). The highest AUC was 0.716 for the OC level for progression at LS. The levels of OC predicted progression at LS with sensitivity of 0.76, specificity of 0.63, and positive predictive value of 0.52 at the cutoff value of >1.41 nmol/l.

The predictive value of a multivariate model generated according to the logistic regression analysis incorporating OC level, age, height, weight, and BMD at baseline for progression at LS (AUC of 0.737) was not significantly different from that of OC alone. The AUCs of OC and tDPD for progression at DR were significantly higher in the multivariate models, although the contribution of either OC or tDPD tended to be insignificant in the models used (data not shown).

Discussion

The OC levels showed statistical significance in predicting which osteopenic woman would progress to the osteoporotic level at LS. The tDPD levels showed a similar but more modest predictive value for progression. As predictive markers, BAP had some value, whereas CTX and fDPD lacked value. In addition, we detected no predictive value for progression at TH for any of the biochemical markers of bone turnover evaluated in this study.

We measured the levels of free and total deoxypyridinoline. Previously, the levels of tDPD were measured by high-performance liquid chromatography [33], but fDPD has become the predominant marker since the fDPD ELISA was introduced to the market [30]. However, fDPD showed no remarkable value in predicting progression at any of the skeletal sites in the present cohort of osteopenic women, whereas tDPD showed significant value in this respect. Similarly, the tDPD (but not fDPD) levels predicted the extent of bone loss in perimenopausal women [21]. There-

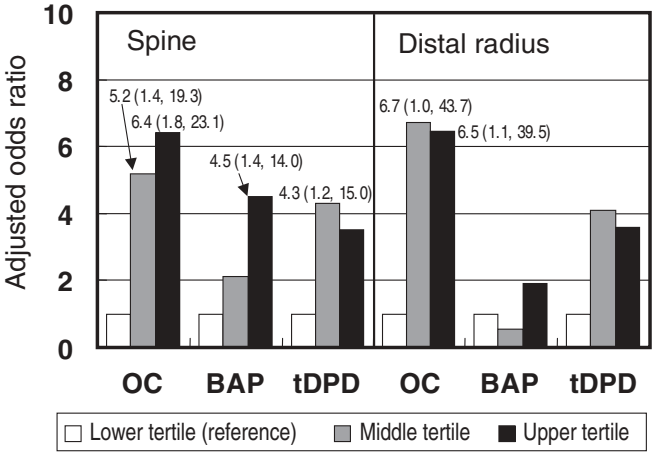

Fig. 1. Odds ratios for progression to osteoporosis, as adjusted for age, height, weight, and bone mineral density (BMD) at baseline, in women with lower-level osteopenia with different tertile levels of osteocalcin (*OC*), bone-specific alkaline phosphatase (*BAP*), or total deoxypyridinoline (*tDPD*) at baseline. The odds ratios and associated 95% confidence intervals (in parentheses) are shown when the odds ratios are significantly different from unity. The lower level of osteopenia is defined as BMD ≥70% and <75% of the young adult mean. Data from the JPOS Cohort Study

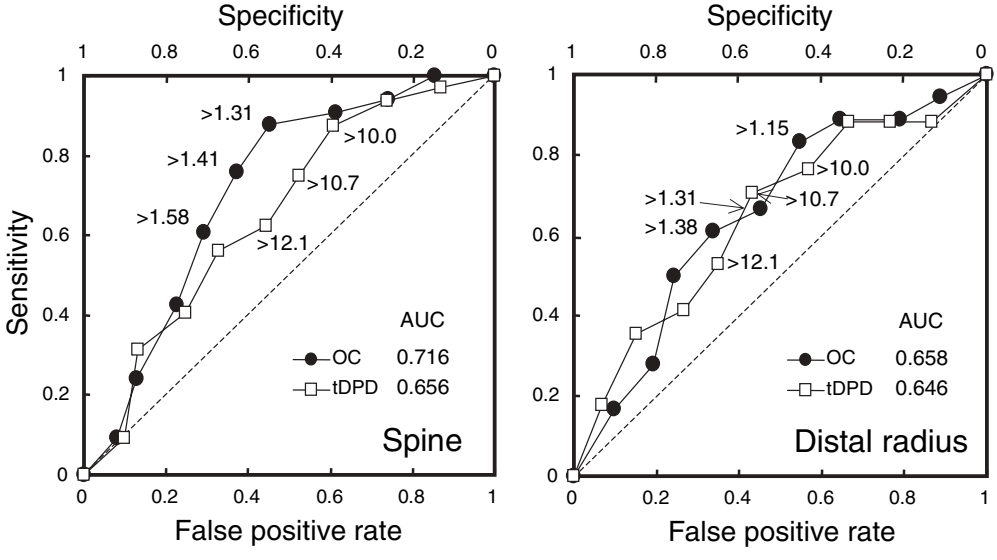

Fig. 2. Receiver operating characteristics analysis of the levels of osteocalcin (OC) and total deoxypyridinoline (tDPD) at baseline for predicting progression to osteoporosis of the spine and distal radius in lower-level osteopenia women. The cutoff levels for OC are shown in nmol/l and for tDPD in nmol/mmol Cr. *AUC*, area under the curve. The lower level of osteopenia is defined as BMD ≥70% and <75% of the young adult mean. Data from the JPOS Cohort Study

fore, it is more important to measure tDPD than fDPD for predictions of BMD changes. On the other hand, CTX showed no predictive value for progression to osteoporosis in this study, although there was a fairly strong association of CTX levels with bone loss in perimenopausal women [21]. Thus, care should be taken to match the bone turnover marker to the desired predictive objective in the specific individual.

In the present study, 34.7% of the osteopenic women with BMD ≥70 and <75% of YAM at LS progressed to the osteoporotic level within 3 years. Using the baseline cutoff of >1.41 nmol/l for OC, it would have been possible to identify those patients with sensitivity of 76% who would show disease progression. Disease progression in these women could have been largely prevented by the administration of alendronate or risedronate, because their BMD values were expected to increase by 5% in the first year of treatment and at a lower rate in subsequent years [34]. The relative and absolute risk reductions for progression under the present conditions are calculated to be 76% and 26%, respectively; this means that four patients need to be treated to prevent one progression among those four subjects [the number needed to treat (NNT) is 4], which is considered to be quite efficient. On the other hand, we had the false-positive rate of 37% at the same cutoff and, therefore, 24% of the cohort members would be screened and treated unnecessarily. Nevertheless, these patients would derive benefit rather than harm from treatment, because their BMD values would be increased and their fracture risk decreased to a substantial extent by the treatment [1].

Surprisingly, we failed to obtain any significant association between the levels of biochemical markers of bone turnover and progression to osteoporosis at TH. The prevention of hip fracture is the most important objective in the management of osteoporosis. BMD at the hip is one of the strongest predictors for this fracture [35]. It would be extremely valuable to be able to predict from assessments of the levels of bone turnover markers which women with TH osteopenia would progress to the osteoporotic level of BMD. However, in our cohort of postmenopausal women, no bone turnover marker at baseline predicted the extent of bone loss at TH during the subsequent 3 or 6 years [21]. Other studies have given similar unfavorable results [19,20]. Currently, we do not know the reason for these findings. Biochemical markers of bone turnover represent the status of bone turnover of the whole skeleton. It is possible that the fraction of turnover attributable to the hip bone may not be sufficiently large to produce a detectable change in marker levels.

There are several limitations to this study. First, we did not set the fracture risk as the outcome variable and, therefore, we do not know to what extent the present results contribute to the reduction of fractures. Second, we did not evaluate the predictive value of relatively new markers, such as urinary type I collagen cross-linked N-terminal telopeptide [36], the α-isomer of CTX [37], serum CTX [38], the amino-terminal propeptide of type I procollagen [39], and undercarboxylated osteocalcin [40], because the relevant assays were not commercially available at the time of our baseline study. Third, the results presented here may not be applicable to other cohorts. A validation study is necessary to put the present results into practice.

In spite of these limitations, the present study has several advantages in study design, such as a representative sampling from the general population and acceptable participation rates at baseline and follow-up, suggesting that our samples had relatively smaller selection bias in comparison with hospital samples or volunteers and that it is appropriate to apply our results to the general population.

In summary, the biochemical markers of bone turnover OC and tDPD may be useful in predicting which osteopenic woman will progress to osteoporosis, independently of subject age and body size at baseline. Although a validation study is necessary, a woman with a spine BMD ≥70 and <75% of YAM should be offered serum OC measurement, and if her OC level exceeds 1.41 nmol/l, she should be treated as a candidate for drug therapy for osteoporosis.

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